Amendments to the Drawings:

The attached sheets of drawings includes changes to FIG. 1 and FIG. 2. These sheets replace the original sheets including FIGS. 1 and 2. Figures 1 and 2 have been amended to conform the sequences to those in the Sequence Listing. Accordingly, no new matter is introduced by these amendments.

Attachment: Replacement Sheets

REMARKS

Claims 19-33 are currently pending in the application. Applicants acknowledge that claims 34-51 have been withdrawn in the Office Action as being drawn to a nonelected invention.

Claim 19 has been amended to indicate "nucleic acid sequences present within the protein envelope." Support for this amendment is found in the specification at, *inter alia*, page 3, paragraph 12, as discussed below. Claim 20 has been amended herein to clarify a typographical error to better define that the virus protein is derived from a virus selected from the listed group. Claim 23 has been amended to recite "the large surface protein of HBV," which is the meaning of LHBs as described in the specification at, *inter alia*, page 1, paragraph 5 (substitute specification). Claims 30 and 32 have been amended to recite "consists of" instead of "has." Claim 33 (and withdrawn claim 34) have been amended to recite "produced by the cotransfected cells of step (a)," to insert a new step (b) reciting "cultivating the cotransfected cells of step (a) to produce the particle," and to better define the claimed invention. Support for these amendments is found, *inter alia*, in the specification at page 6, paragraph 26; page 11, paragraph 41; and page 12, paragraph 46. In addition, the claims have been amended to change the dependencies to correct for the fact that the claims were renumbered by the Examiner. Accordingly, Applicants respectfully submit that no new matter has been added by these amendments.

With regard to the Examiner's inquiry regarding claim 18, Applicants have cancelled claim 18 herein without prejudice or disclaimer of the subject matter claimed therein.

Figures 1 and 2 have been amended to conform the sequences to those in the Sequence Listing. Accordingly, no new matter is introduced by these amendments. These changes were proposed in the Preliminary Amendment filed November 30, 2001, and accepted by the Examiner as indicated in the Office Action at page 3. However, as

corrected drawings were requested by the Examiner, the amendments are being introduced in this Amendment in accordance with the revised amendment rules.

The outstanding rejections are addressed individually below.

1. Objection to Claims 23, 30 and 32 have been overcome

Claims 30 and 32 are objected to under 37 C.F.R. § 1.75 as allegedly being a substantial duplicate of claims 29 and 31, respectively. Claims 30 and 32 have been admended herein to recite "consists of" instead of "has." Accordingly, Applicants respectfully submit that claims 30 and 32, as amended, are not a substantial duplicate of claims 29 and 31, respectively, which recite the language "comprises."

Claim 23 is objected to because the abbreviation "LHBs" should be spelled out the first time it appears in the claims. Claim 23 has been amended to recite "the large surface protein of HBV (LHBs)." Accordingly, Applicants respectfully submit that claim 23 as amended is appropriate.

Applicants respectfully submit that the objections to claims 23, 30, and 32 have been overcome. Applicants respectfully request that the objections to these claims be reconsidered and withdrawn.

2. Claims are definite under 35 U.S.C. § 112, second paragraph.

The pending claims have been rejected for various reasons under 35 U.S.C. § 112, second paragraph. More specifically:

a) "Cell permeability-mediating peptide" is definite

Claims 19-33 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Applicants respectfully traverse this rejection.

The Office Action states that it is not clear what "cell permeability-mediating peptide" is or how this differs from normal viral proteins that allow for attachment and entry of virus. (Office Action, pages 4-5)

Applicants respectfully submit that the term "cell permeability-mediating peptide" is clear and definite. The specification defines "cell permeability-mediating peptide" as including "any peptides capable of mediating a cell permeability for substances, in particular proteins." (Substitute Specification, page 2, paragraph 7) Furthermore, the specification provides at least one nonlimiting example of such a peptide, which is SEQ ID NO: 20. In addition, Applicants respectfully submit that the specification makes it clear that cell permeability-mediating peptides can include normal viral proteins that allow for attachment and entry of a virus. This is indicated in the specification at, *inter alia*, page 1, paragraph 5, which teaches that the cell permeability-mediating peptide can be that present in the region of PreS2 of LHBs, which is part of the large surface protein of HBV.

Accordingly, Applicants respectfully submit that this term is definite, and as such respectfully request that this rejection be reconsidered and withdrawn.

b) "Nucleic acid present in the protein envelope" is definite.

The Office Action states that it is not clear if the meaning of "nucleic acid present in the protein envelope" in claim 1(b) means contained within the particle or if the nucleic acid sequences are part of the envelope. (Office Action, page 5) (Applicants assume this refers to the phrase "nucleic acid sequences present in the protein envelope" in claim 19(b).)

The specification clearly indicates at page 3, paragraph 12 that the virus specific packaging signal, which is part of each of the nucleic acids referred to in claim 19(b), indicates a signal sequence by means of which the nucleic acids are packaged into the protein envelope of a particle. Claim 19 has been amended to clarify this relationship.

Accordingly, Applicants submit that this term is definite, and respectfully request that this rejection be reconsidered and withdrawn.

c) "Derived" is definite

The Office Action states that claim 20 is not clear as to the metes and bounds of "derived," and how much is changed from the original protein. (Office Action, page 5) Applicants respectfully traverse this rejection.

Applicants respectfully submit that the meaning of "derived" is clear when read in light of the specification. The specification at pages 2-3, paragraph 10, describes a "virus protein" as "any protein of a virus mentioned above which can be present in its entirety or partially in a fusion protein together with a cell permeability-mediating peptide and a heterologous cell-specific binding site in the form of a further peptide. The protein can also already contain the cell permeability-mediating peptide. An example of one such protein is LHBs." Thus, the definition of "virus protein" indicates the way in which such a protein could be "derived" from its original protein.

Accordingly, the claim term "derived" is clear when read in light of the specification. Therefore, Applicants respectfully request that this rejection be reconsidered and withdrawn.

d) "Cells containing a hepatitis B virus genome, wherein the cells do not express LHBs" is definite

The Office Action states that claim 33 is not clear as to what is meant by "cells containing a hepatitis B virus genome, wherein the cells do not express LHBs" because a cell containing an HBV genome would produce LHBs, or whether the genome does not produce its own. (Office Action, page 5)

Applicants respectfully submit that this language is clear when read in light of the specification. Example 1 describes the preparation of a particle according to the invention which contains a fusion protein including an LHBs and a heterologous binding site. However, Example 1 makes clear that in the method of this Example, the cells containing a hepatitis B virus genome do not express LHBs. The specification states in Example 1 that in the example being described, the "expression vector codes

for all HBV-specific proteins *with the exception of LHBs"* and eventually is used to create a cell line expressing all HBV-specific proteins with the exception of LHBs. (Substitute Specification, page 9, paragraph 36 and page 11, paragraph 40) (emphasis added) In Example 1, this cell line is then transfected with additional vectors such that the particles produced include all of the HBV-specific proteins *"with the exception of LHBs,* which is replaced by a RGD-LHBs." (Substitute Specification, page 11, paragraph 41) (emphasis added). Although additional methods can be used, this example indicates that claim 33 is intended to refer to "cells containing a hepatitis B virus genome, wherein the cells do not express LHBs." Although Applicants disagree with this rejection, claim 33 has been amended herein to clarify this language in order to better define the claimed invention. Applicants aver that this amendment does not change the scope of the claim.

Thus, Applicants submit that this language is clear and definite. Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

e) Claim 33 as amended indicates that the particles of step (a) are isolated in step (b)

The Office Action states that claim 33 is also rejected because there is no indication that the particles of step (a) are made to be isolated in step (b). (Office Action, page 5) (Applicants note that new step (b) was inserted between previous steps (a) and (b)).

Claim 33 (and withdrawn claim 34) have been amended to recite as step (c), "isolating and purifying the particles produced by the cotransfected cells of step (a)." Accordingly, Applicants respectfully submit that this rejection has been overcome. Applicants respectfully request that this rejection be reconsidered and withdrawn.

3. Claims 19-25, 27-29, 31, and 33 comply with the written description requirement.

Claims 19-25, 27-29, 31, and 33 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Applicants respectfully traverse this rejection.

The Office Action states that the term "cell permeability-mediating peptide" is not defined in such a way to allow one of ordinary skill in the art to know what the structural basis is. The Office Action states that the term is defined by function only and that the specification provides one example. The Office Action further states that there is no indicated structure described that can be used to determine all possible peptides that have this function. The Office Action concludes that only SEQ ID NO:20, but not the full breadth of the claims, meets the written description requirement. (Office Action, page 6)

M.P.E.P. § 2163 (I) states that to

> satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention[at the time the application was filed]. . . . Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" . . . or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention.

M.P.E.P. § 2163 (I)(A) states that there "is a strong presumption that an adequate written description of the claimed invention is present when the application is filed." (Applicants submit that the term "cell permeability-mediating peptide" was present in the original claims as filed.) M.P.E.P. § 2163 (II)(A)(2) states that generally "there is an inverse correlation between the level of skill and knowledge in the art and the specificity of disclosure necessary to satisfy the written description requirement. Information which is well known in the art need not be described in detail in the

specification." M.P.E.P. § 2163 (III)(A) states that a *prima facie* case for lack of written description is established by "providing reasons why a person skilled in the art at the time the application was filed would not have recognized that the inventor was in possession of the invention as claimed in view of the disclosure of the application as filed."

Applicants respectfully submit that there is not a *prima facie* case for lack of written description. The specification provides a definition of the term "cell permeability-mediating peptide" at page 2, paragraph 7, which states that such a peptide includes "any peptides capable of mediating a cell permeability for substances, in particular proteins." The specification provides SEQ ID NO:20 as a nonlimiting example of such a cell permeability-mediating peptide. Furthermore, SEQ ID NO:1, which describes the amino acid sequence for a fusion protein, includes a similar cell permeability-mediating peptide sequence in which the "leucine" has been replaced by "isoleucine."

Furthermore, the specification indicates at page 4, paragraph 14 that the fusion protein can differ from the amino acid sequence of FIG. 2 by one or more amino acids. The term "an amino acid sequence differing in one or more amino acids" is defined at page 4, paragraph 16 as indicating that "this amino acid sequence specifies a fusion protein which has comparable elements and functions as the fusion protein in Fig. 1 or figure 2 but which differs from the amino acid sequence of Fig. 1 or Fig. 2 up to 20%, preferably 10%."

In addition, Examples 1 and 2 at pages 9-12 demonstrate the preparation of a particle according to the invention.

Accordingly, Applicants respectfully submit that a person skilled in the art at the time the application was filed would have recognized that the inventor was in possession of the invention as claimed in view of the disclosure of the application as filed. Furthermore, one of skill in the art would have recognized that Applicants had

more than one representative sequence for a cell permeability-mediating peptide in their possession at the time that the application was filed.

Therefore, Applicants submit that the term "cell permeability-mediating peptide" does not lack written description. Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

4. Claims 19, 20, and 33 are not anticipated under 35 U.S.C. § 102(b) by Rosenberg.

Claims 19, 20, and 33 stand rejected as allegedly being anticipated under 35 U.S.C. § 102(b) by Rosenberg (WO 97/24453). Applicants respectfully traverse this rejection.

M.P.E.P. § 2131 quotes that a "claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." M.P.E.P. § 2121.01 quotes that in "determining that quantum of prior art disclosure which is necessary to declare an applicant's invention 'not novel' or 'anticipated' within section 102, the stated test is whether a reference contains an 'enabling disclosure'" and states that a "reference contains an 'enabling disclosure' if the public was in possession of the claimed invention before the date of invention." (citation omitted)

Claim 19 recites a particle comprising a protein envelope with a fusion protein, the fusion protein comprising a virus protein, a cell permeability-mediating peptide, and a heterologous cell-specific binding site, and with nucleic acid sequences present within the protein envelope, each of the nucleic acid sequences comprising a sequence encoding a virus-specific packaging signal and a sequence encoding a structural gene. Claim 20 recites various viruses from which the virus protein can be derived, and claim 33 recites a method for the preparation of the particle.

Although Applicants do not necessarily agree with the description of Rosenberg provided in the Office Action, Applicants note that in contrast to the cited claims,

Rosenberg does not disclose that the nucleic acid sequences present within the protein envelope comprise a sequence encoding a virus-specific packaging signal. In addition, Rosenberg does not enable the present invention. Rosenberg provides no working examples (either *in vitro* or *in vivo*) indicating that the polypeptides, particles or methods disclosed therein would work. Furthermore, the examples recited do not provide specific detail regarding how to perform the experiments to create the disclosed particles and chimeric proteins.

Accordingly, Rosenberg does not anticipate claims 19, 20, and 33.

In addition, with regard to claim 33, Rosenberg does not teach a method for the preparation of the particle of the present invention, wherein the fusion protein contains an LHBs and a heterologous cell-specific binding site. In this respect, Rosenberg does not teach a method comprising (a) cotransfecting cells containing a hepatitis B virus genome and not expressing LHBs, with a first expression vector and a second expression vector, the first expression vector coding for a fusion protein comprising an LHBs and a heterologous cell-specific binding site, and the second expression vector comprising a virus-specific packaging signal and a structural gene; (b) cultivating the cotransfected cells of step (a) to produce the particle; and (c) isolating and purifying the particles produced by the cotransfected cells of step (a). In fact, the only reference to HBV appears to be a note by the drafter of the patent that was mistakenly left in the application (See page 14, line 18).

Therefore, Applicants submit that Rosenberg does not anticipate claims 19, 20, and 33 under 35 U.S.C. § 102(b). Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

5. *Claims 19-25 are not anticipated under 35 U.S.C. § 102(b) by Schodel*

Claims 19-25 stand rejected as allegedly being anticipated under 35 U.S.C. § 102(b) by Schodel. Applicants respectfully traverse this rejection.

The Office Action states that Schodel discloses a particle that comprises a protein envelope with a fusion protein comprising a virus protein, a permeability mediating peptide, and a heterologous cell specific binding site (specific T-cell recognition), and contains within it a structural gene. (Office Action, page 7) Applicants respectfully disagree.

The HBcAg-CS1 and HBcAg-CS2 hybrids disclosed in Schodel do not contain a heterologous cell-specific binding site. A "cell-specific binding site" is defined in the specification at page 2, paragraph 8 as including "any binding sites of proteins and other small molecules via which the respective proteins or molecules can bind to cells." Although Schodel discusses at page 95 the T cell recognition of HBcAg-CS hybrid particles and that Th sites can be functionally included in hybrid HBcAg particles in at least the internal site, these Th sites act as epitopes for the T cells to recognize, not as cell-specific binding sites. Schodel does not disclose a heterologous "cell-specific binding site" as part of the fusion protein.

In addition, Schodel does not disclose a cell permeability-mediating peptide or that nucleic acids are present within the protein envelope, each nucleic acid sequence comprising a sequence encoding a virus-specific packaging signal and a sequence encoding a structural gene.

Thus, Applicants submit that claims 19-25 are not anticipated under 35 U.S.C. § 102(b) by Schodel. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

CONCLUSIONS

In view of the arguments set forth above, Applicants respectfully submit that the rejections contained in the Office Action mailed on June 17, 2003, have been overcome, and that the claims are in condition for allowance.

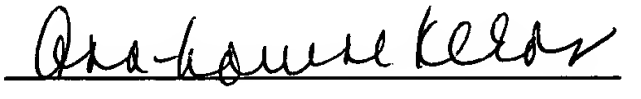
Applicants enclose a Petition for a Three Month Extension of Time pursuant to 37 C.F.R. § 1.136, until December 17, 2003, to respond to the Examiner's Office Action mailed on June 17, 2003. Please charge our Deposit Account No. 08-0219 the $950.00 fee for this purpose.

Applicant also encloses herewith a Supplemental Information Disclosure Statement in accordance with 37 C.F.R. § 1.97(c)(2). Please charge Deposit Account No. 08-0219 the $180.00 fee for this submission.

No other fees are believed to be due in connection with this response. However, please charge any underpayments or credit any overpayments to Deposit Account No. 08-0219.

If the Examiner believes that any further discussion of this communication would be helpful, please contact the undersigned at the telephone number provided below.

Respectfully submitted,



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December 17, 2003
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Attachments: Replacement Figures 1 and 2